Simeprevir plus Sofosbuvir

Criteria for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive simeprevir-based regimen without local adjudication.*

☐ Decompensated liver disease (i.e., Child-Pugh score ≥7, MELD score >18, and/or clinical manifestations)
☐ Documented ongoing nonadherence to prior medications, medical treatment or failure to complete HCV disease evaluation appointments and procedures or patient is unable to commit to scheduled follow-up/monitoring for the duration of treatment
☐ Previous virologic failure with a NS3-4A protease inhibitor containing regimen (intolerance does not constitute failure)
☐ Known hypersensitivity to direct acting antiviral(s) or any other component of direct acting antiviral based-regimen
☐ Coadministration with moderate or strong inducers or inhibitors of cytochrome P450 3A
☐ Co-administration with amiodarone (refer to Issues for Consideration)
☐ Patients with severe renal impairment (<30mL/min), end-stage renal disease or on hemodialysis.
☐ Patient with recurrent post-liver transplant HCV infection

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

☐ Treatment regimen and duration **according to the dosage and administration section below**
☐ Under care of and/or in collaboration with an experienced VA HCV practitioner
☐ Adherence counseling performed including laboratory follow-up and documented understanding by patient
☐ Chronic Infection with Hepatitis C Virus **Genotype 1**

Dosage, Administration

Population	FDA approved interferon-free regimens	Total treatment duration
Treatment-naïve and treatment-experienced* patients without cirrhosis	Simeprevir 150mg orally once daily with food *plus* sofosbuvir orally 400mg once daily	12 weeks
Treatment-naïve and treatment-experienced* patients with cirrhosis	Simeprevir 150mg orally once daily with food *plus* sofosbuvir orally 400mg once daily	24 weeks**

*Treatment-experienced patients include prior relapsers, prior partial responders and prior null responders who failed prior IFN-based therapy.
****Refer to Issues for consideration for alternative treatment options.**

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving Hepatitis C therapy, the following monitoring is recommended for simeprevir based-regimen:

- **Rash**: Serious reactions have occurred with simeprevir. Rash occurred most frequently in the first 4 weeks of therapy but can occur at any time during treatment. Patients with mild to moderate rashes should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, simeprevir should be discontinued. Patients should be monitored until the rash has resolved.
- **Photosensitivity:** Serious reactions have occurred with simeprevir. Use sun protective measures and limit sun exposure. Consider discontinuation of simeprevir if a photosensitivity reaction occurs; patients should be monitored until the reaction has resolved.
- **Careful virologic monitoring** should be assessed to avoid the emergence of resistance. Patients should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.
- **Sustained Viral Response (SVR) or relapse** should be determined by measurement of HCV RNA at the end of therapy and 12 weeks thereafter.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.

Issues for Consideration

Treatment Considerations:

- **Alternative treatment options: For genotype 1 cirrhotic patients who are currently receiving simeprevir plus sofosbuvir, an alternative option is to complete 12 weeks of simeprevir plus sofosbuvir and assess for SVR12. If relapse occurs, offer retreatment with 12 weeks of ledipasvir /sofosbuvir plus ribavirin.** In a randomized, double-blind study ledipasvir/sofosbuvir plus ribavirin for 12 weeks was compared to ledipasvir/sofosbuvir for 24 weeks in cirrhotic patients who have previously failed protease-inhibitor based triple therapy; SVR was achieved in 96% (74/77) of patients treated with ledipasvir/sofosbuvir plus ribavirin for 12 weeks and in 75/77 (97%) of patients treated with ledipasvir/sofosbuvir for 24 weeks. In the COSMOS study in patients with Metavir F3, SVR12 was achieved in 94% of patients who received sofosbuvir+simeprevir+ribavirin for either 12 weeks (15/16) or 24

weeks (16/17). SVR was achieved in 100% of patients who received sofosbuvir+simeprevir for either 12 weeks (7/7) or 24 weeks (6/6). In patients with Metavir F4 who received sofosbuvir+simeprevir+ribavirin, SVR12 was achieved in 91% of patients receiving 12 weeks of treatment (10/11) and in 92% of patients receiving 24 weeks (12/13) of treatment. SVR was achieved in 86% (6/7) of patients who received sofosbuvir+simeprevir for 12 weeks and in 100% (10/10) of those who received this regimen for 24 weeks; however, this represents a difference of only 1 patient.

- **Chronic HCV-infected patients with minimal fibrosis** (METAVIR stage 0, 1 based on an adequate liver biopsy specimen) are at lower risk for developing advanced liver disease in the short-term. After a thorough discussion of prognosis and treatment options, the provider and patient may agree to observation and defer treatment. Treatment should be reconsidered if liver disease progresses.
- **In genotype 1a patients:** The prescribing information states prior to initiation of treatment with simeprevir with sofosbuvir, screening patients infected with HCV genotype 1a for the presence of virus with the NS3 Q80K polymorphism is not strongly recommended but may be considered.

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV**: The FDA package labeling does not address HIV/HCV co-infected patients. However, the use of sofobuvir plus simeprevir (+/– ribavirin) for 12 weeks can be considered in GT1 co-infected patients, particularly those who are HCV treatment experienced.
- **Liver transplant:** Limited efficacy and safety data are available in pre- or post-transplant. While simeprevir+sofosbuvir ± ribavirin for 12 weeks was evaluated in post-transplant patients and an SVR of 91% was obtained in the 66 patients for which data were available, drug-drug interactions with certain immunosuppressants exist. Concomitant use of simeprevir with cyclosporine results in significantly increased simeprevir concentrations (approximately 6-fold); simeprevir should not be coadministered with cyclosporine. Routine monitoring of tacrolimus levels is recommended since tacrolimus levels can be reduced when coadministered with simeprevir. Alternative treatment with ledipasvir/sofosbuvir+ribavirin should be considered to minimize potential for interactions.
- **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information states that no dosage adjustments are needed for either drug.
- **Substance or Alcohol Use**: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists as needed. **Thus, automatic disqualification of patients as treatment candidates based on a specific length of abstinence is unwarranted and is strongly discouraged**.
- **Mental Health Conditions:** Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, PTSD), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis.
- **Renal Impairment:**
    - Simeprevir: No dose adjustment of simeprevir is required in patients with mild, moderate or severe renal impairment
    - Sofosbuvir: No dosage adjustment is necessary for patients receiving sofosbuvir with mild or moderate renal impairment; the safety and efficacy of sofosbuvir has not been established in patients with severe renal impairment (eGFR<30mL/min), end-stage renal disease or on hemodialysis and therefore no dose recommendation can be provided. The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min.
- **Hepatic Impairment:**
    - No dosage adjustment is necessary for patients with mild hepatic impairment receiving simeprevir or sofosbuvir. No safety and efficacy available for use of simeprevir in HCV-infected patients with moderate or severe hepatic impairment. HCV-uninfected subjects with moderate or severe hepatic impairment had AUC_{24} of simeprevir 2.4- and 5.2-fold higher, respectively. The prescribing information states that no dose recommendation can be given for patients with moderate severe hepatic impairment (Child-Pugh Class B) due to modest increases in simeprevir exposures; simeprevir is not recommended for patients with severe hepatic impairment (Child-Pugh Class C) due to substantially higher simeprevir exposures. In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity.
- **East Asian ancestry:** HCV-infected patients of East Asian ancestry had AUC_{24} of simeprevir 3.4-folder higher. Insufficient data to recommend reduce dose in this population; risk and benefits should be considered prior to use.
- **Sulfa Allergy:** Simeprevir contains a sulfonamide moiety. In subjects with a history of sulfa allergy (n=16), no increased incidence of rash or photosensitivity reactions has been observed. However, there are insufficient data to exclude an association between sulfa allergy and the frequency or severity of adverse reactions observed with the use of simeprevir.

Drug-interactions:

- The primary enzyme involved in the biotransformation of simeprevir is CYP3A; co-administration of simeprevir with agents that are moderate or strong inducers or inhibitors of CYP3A is not recommended. Refer to prescribing information for additional information.
- Sofosbuvir is a substrate of drug transporter P-gp; drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations. Refer to prescribing information for additional information.
- **Bradycardia with amiodarone coadministration:** Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with simeprevir and another direct acting antiviral is not recommended. For patients taking amiodarone who have no other alternative treatment options and who will be co-administered simeprevir in combination with sofosobuvir, the prescribing information recommends the following: counsel patients about the risk of serious symptomatic bradycardia; cardiac monitoring in an in-patient setting for the first 48 hours of coadminstration is recommended, after which outpatient or self-monitoring of the heart rate would occur on a daily basis through at least the first 2 weeks of treatment. Since amiodarone has a long half-life, important drug interactions may occur for some time after discontinuation.

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use.

- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov

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